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Claim 16 stands rejected for an alleged lack of novelty. The Examiner cites Wright et al. (Gene Vol. 49, pp. 311-321, 1986). The Examiner alleges that "Wright et al. disclose of microorganisms comprising dual origin plasmids, the disclosure of Wright et al. is deemed to be a 'modification' of the vector pMEG-771, and consequently deemed to anticipate the claimed invention."

Whether the rejection is directed at claim 16 or 17, Wright do not anticipate the claimed invention. Claim 16 does not specifically recite pMEG-771. Wright teach a two ori's plasmid. In Wright, the expression of the desired gene is controlled by a promoter P_{trp}, which is repressed by the chromosomal trpR gene (trp repressor). As the temperature increases, the high copy replication is derepressed, and the trpR gene is unable to repress the P_{trp} promoter. This results in expression of the desired foreign gene. For example, on p. 317, col.1, of Wright, the authors stated that *trpR* cannot repress the expression of the desired gene product, prochymosin, at 42 °C.

Because claims 16 and 17 depend from claim 15, which recite a second control sequence, P_{trc}, and a second repressor, *Lac I*, claims 16 and 17 necessarily possess these limitations. Claim 16 also recite a C2 repressor. Any "modifications" of pMEG-771 would require inclusion of these limitations. As Wright do not teach or suggest each and every element of claim 16 or 17, Wright cannot anticipate the claimed invention. Applicants respectfully request withdrawal of this rejection.

Claims 7-8, 12, 14-15, 17-22, and 32-37 are objected to as depending upon an objected claim. Applicants believe that all of the above rejections and objections have been overcome or obviated. Applicants respectfully request that the objections to dependent claims 7-8, 1, 14-15, 17-22, and 32-37 be withdrawn.

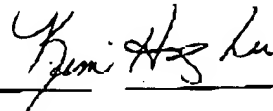
Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot by the above amendments and remarks. Applicant therefore

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respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, he is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,



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CLAIM AMENDMENTS

1. (cancelled) A microorganism comprising a regulated antigen delivery system (RADS), wherein the RADS comprises

- (a) a vector comprising (1) a site for insertion of a gene encoding a desired gene product;
- (2) a first origin of replication (ori) conferring vector replication using DNA polymerase III; and
- (3) a second ori conferring vector replication using DNA polymerase I,

wherein the second ori is operably linked to a first control sequence repressible by a first repressor, and wherein the runaway vector does not comprise a phage lysis gene; and

- (b) a gene encoding a first repressor operably linked to a first activatable control sequence.

2. (previously amended) A microorganism comprising a regulated antigen delivery system (RADS), wherein the RADS comprises (a) a vector comprising (1) a gene encoding a desired gene product inserted into a site for insertion of a gene encoding a desired gene product, wherein the gene encoding the desired gene product is operably linked to a second control sequence; (2) a first origin of replication (ori) conferring vector replication using DNA polymerase III; and (3) a second ori conferring vector replication using DNA polymerase I,

wherein the second ori is operably linked to a first control sequence repressible by a first repressor, and wherein the runaway vector does not comprise a phage lysis gene; and

- (b) a gene encoding a first repressor operably linked to a first activatable control sequence.

3. (original) The microorganism of claim 2, wherein the first control sequence and the second control sequence are the same sequence.

4. (original) The microorganism of claim 2, wherein the first control sequence and the second control sequence are different sequences.

5. (previously amended) The microorganism of claim 2, wherein the repressor is selected from the group consisting of LacI repressor and C2 repressor, and wherein the second control sequence is repressible by a second repressor.

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6. (currently amended) The microorganism of claim 2, wherein
 - (a) the vector is a plasmid;
 - (b) the desired gene product is an antigen and
 - (c) the microorganism is an [attenuated derivative of a pathogenic bacterium]
attenuated bacterium.
7. (original) The microorganism of claim 6, wherein the microorganism is a *Salmonella* sp.
8. (original) The microorganism of claim 6, wherein the first activatable control sequence is *araCP_{DAD}*.
9. (cancelled) The microorganism of claim 6, further comprising a balanced lethal host-vector system consisting of a lack of a functioning essential gene on the chromosome and a recombinant functioning copy of the essential gene on the vector.
10. (cancelled) The microorganism of claim 9, wherein the essential gene is an *asd* gene.
11. (cancelled) The microorganism of claim 10, wherein the *asd* gene is inactivated by the insertion of a repressor gene operably linked to *araCP_{RAID}*.
12. (original) The microorganism of claim 6, further comprising an inactivating mutation in a native gene selected from the group consisting of *cya*, *crp*, *phoPQ*, *ompR*, *galE*, *cdt*, *hema*, *aroA*, *aroC*, *aroD* and *htrA*.
13. (currently amended) The microorganism of claim 6, wherein the first ori is a pSC ori, and the second ori is a pUC ori.

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14. (original) The microorganism of claim 6, wherein the first control sequence is P₂₂ P_R and the first repressor is C2 repressor.

15. (original) The microorganism of claim 6, wherein the second control sequence is P_{trc} and wherein the second control sequence is repressible by a second repressor, and wherein the second repressor is a LacI repressor.

16. (original) The microorganism of claim 15, wherein the first control sequence is P₂₂ P_R; the first repressor is C2 repressor; the first ori is a pSC ori, and the second ori is a pUC ori.

17. (original) The microorganism of claim 16, wherein the vector is pMFG-771, or modifications thereof, with a gene encoding an antigen.

18. (original) The microorganism of claim 6, wherein the antigen is selected from the group consisting of Ery65 and SeM.

19. (original) The microorganism of claim 6, wherein the desired gene product is operably linked to a eukaryotic control sequence.

20. (original) The microorganism of claim 19, further comprising a $\Delta endA$ mutation.

21. (original) A runaway vector comprising the vector in the microorganism of claim 19.

22. (original) The microorganism of claim 6, which exhibits delayed RADS characteristics, wherein the delayed RADS characteristics are conferred by an alteration selected from the group consisting of: mutations that delay the loss of activator molecules by metabolism and/or leakage, a mutation or insertion to increase repressor concentration, and inclusion of a vector control sequence with binding sites for more than one repressor and/or vector sequences encoding repressor molecules that act on a vector control sequence.

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23. (cancelled) A method of producing a desired gene product, comprising, in order,
- (a) engineering a gene encoding the desired gene product into the vector in the microorganism of claim 6, wherein the microorganism comprises control sequences that repress expression of the second ori under a first environmental condition, but in which the expression of the second ori is derepressed under a second environmental condition;
 - (b) culturing the microorganism of step (a) under the first environmental condition; and
 - (c) culturing the microorganism with runaway vector of step (a) under the second environmental condition for a time sufficient to produce the desired gene product.
24. (cancelled) The method of claim 23, wherein the desired gene product is an antigen.
25. (cancelled) The method of claim 24, wherein the first environmental condition comprises the presence of arabinose and the second environmental condition comprises the absence of arabinose.
26. (cancelled) The method of claim 25, wherein the first environmental condition comprises *in vitro* culture conditions and the second environmental condition comprises conditions inside of a vertebrate.
27. (cancelled) The method of claim 26, wherein
- (a) the first ori is a pSC ori;
 - (b) the second ori is a pUC ori, which is operably linked to a repressing control sequence consisting of P22 P_R;
 - (c) the product control sequence is P_{UC};
 - (d) the microorganism comprises a gene encoding a first repressor operably linked to a first activatable control sequence, wherein the first repressor is C2; and

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(e) the microorganism comprises a gene encoding a second repressor operably linked to a second activatable control sequence, wherein the second repressor is LacI;

(f) the microorganism comprises a chromosome without a functional *asd* gene and the runaway vector comprises a functional *asd* gene; and

(g) the microorganism comprises an inactivating mutation in a native gene selected from the group consisting of *cya*, *crp*, *phoP*, *ompR*, *galE*, *cdt*, *hemA*, *aroA*, *uroC*, *aroD* and *htr*.

28. (cancelled) The method of claim 27, wherein the first environmental condition comprises the presence of arabinose and the second environmental condition comprises the absence of arabinose.

29. (cancelled) The method of claim 28, wherein the microorganism further comprises an inactivating deletion in the *araC*:*BAD* operon and/or the *araE* gene.

30. (cancelled) The method of claim 29, wherein the desired gene product is selected from the group consisting of Ery65 and SeM.

31. (cancelled) The method of claim 29, wherein the desired gene product is operably linked to a eukaryotic control sequence.

32. (original) A vaccine for immunization of a vertebrate, the vaccine comprising the microorganism of claim 6 in a pharmaceutically acceptable carrier.

33. (original) The vaccine of claim 32, wherein the microorganism is a *Salmonella* sp.

34. (original) The vaccine of claim 32, wherein:

(a) the first ori is a pSC ori;

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(b) the second ori is a pUC ori, which is operably linked to a repressing control sequence consisting of P₂₂ P_R;

(c) the product control sequence is P_{trc};

(d) a gene encoding a first repressor operably linked to a first inducible control sequence, wherein the first repressor is C2; and

(e) a gene encoding a second repressor operably linked to a second inducible control sequence, wherein the second repressor is LacI.

35. (original) The vaccine of claim 34, wherein the first activatable control sequence and the second inducible control sequence are both *araCTBAD*.

36. (original) The vaccine of claim 35, wherein the microorganism further comprises an inactivating deletion in the *araCBAD* operon and/or the *araE* gene.

37. (original) A method of inducing immunoprotection in a vertebrate comprising administering the vaccine of claim 32 to the vertebrate.